REMARKS

The Office Action

Claims 1-6, 9, 10, and 21-25 are under examination in this case. All claims stand rejected under 35 U.S.C. § 103. This rejection is addressed below.

Amendments

Claims 1, 9, 10, and 25 have been amended to clarify that the adenoviral vectors recited in the claims include neither adenoviral nor *E. coli* coding DNA sequences. No new matter is added by this amendment.

Examiner Interview

Applicants thank Examiner Whiteman for the helpful telephonic interview of July 26, 2006. The amendments and arguments presented in that interview are reiterated below.

Rejections under 35 U.S.C. § 103(a)

Claims 1-6, 9, 10, and 21-25 stand rejected under 35 U.S.C. § 103 as being unpatentable over Reichel either alone or in various combinations with Kovesdi, Tezel, Funk, or Williams. These rejections are respectfully traversed.

The current claims are directed to a pigment epithelial cell of the eye which includes adenoviral vector DNA having at least one expressed nucleic acid operatively linked to a promoter. Importantly, the vector includes neither adenoviral nor *E. coli* coding DNA sequences. As indicated in Applicants' specification, this vector represents a significant advance in the area of adenoviral vector technology because removal of the adenoviral coding sequences allows the vector to carry very large segments of foreign DNA, while surprisingly the vector is still capable of transducing pigment epithelial cells of the eye. In addition, the absence of *E. coli* vector sequences, which are generally

immunogenic in mammalian hosts, allows for the optimized use of Applicants' claimed vector in therapeutic applications. Neither this vector, its use for transducing pigment epithelial cells of the eye, nor the particular methods for cultivating those transduced cells are suggested by the prior art.

The present rejection primarily relies on Reichel, a review article summarizing the state of the art at the time of its publication. This reference describes a number of gene transfer systems utilized for ophthalmologic applications, some of which involve adenoviral vectors. Two portions of Reichel are cited by the Office. The first passage is at page 7. There, a *non high capacity* adenoviral vector is described for gene transfer into the eye. Disclosure of this vector fails to suggest either the construction or the workability of Applicants' adenoviral system. Notably, the non high capacity Reichel vector at page 7 has both a reduced capacity for foreign genes and also includes viral coding sequence, making it substantially different from the vectors currently claimed and in no way suggesting to one skilled in the art that functional vectors lacking such viral sequences should or could be generated. Moreover, the fact that this non high capacity adenoviral vector that *includes* adenoviral coding sequence could be introduced into retinal pigment epithelium teaches little or nothing about whether a vector *completely lacking* adenoviral coding sequence could be similarly transduced into and maintained in such cells. The Office's reliance on these vectors to suggest Applicants' claimed invention should be withdrawn.

In like manner, the description on page 8 of Reichel also fails to suggest Applicants' claimed invention. There, the system of Kumar-Singh (Hum. Mol. Genet. 7:1893-1900, 1998) is described in which EAMs, vectors that resemble high capacity adenoviral vectors, are utilized. These Kumar-Singh vectors differ significantly from those currently claimed in that Applicants' vectors include no *E. coli* coding sequence. In contrast, as described in Kumar-Singh, the EAM vectors contain several *E. coli* plasmid elements, such as an *E. coli* plasmid backbone, ampicillin resistance gene, and *E. coli*

origin of replication (see Kumar-Singh, page 1894, Fig. 1). Following production, the EAM vector is characterized by extensive genomic variability; monomeric and dimeric structures in head-to-head, head-to-tail, and tail-to-tail orientation are observed (see Kumar-Singh, page 1895, end of last paragraph, and Fig. 4). This genetic variability and the presence of plasmid sequences including a bacterial origin of replication and antibiotic resistance gene reduce the utility of the EAM-based adenoviral vectors for clinical use and highlight the distinction between the currently claimed vectors and the EAMs described by Reichel and Kumar-Singh. As indicated above, Applicants' claimed vectors contain only the adenoviral inverted terminal repeats (ITRs) and adenoviral non-coding DNA, a configuration that results in the production of a vector population that is genetically homogeneous and useful for therapeutic applications.

In addition, particularly with respect to independent claims 10 and 25 and their dependent claims, Applicants point out that the cited Reichel reference, rather than suggesting the claimed invention, teaches away from it. These claims cover methods for producing pigment epithelial cells of the eye transduced with Applicants' adenoviral vectors using particular culturing techniques. The cited Reichel reference, rather than suggesting that adenoviral vectors should be transduced into host cells and cultured (for example, for *ex vivo* therapy) teaches away from this approach. Reichel and Kumar-Singh teach the use of EAMs solely by injection of the viral vector directly into the subretinal space. Neither of the references suggests a transduction of explanted RPE cells containing adenoviral vectors of any type, or indeed the approach of *ex vivo* therapy involving the administration of transduced pigment epithelial cells of the eye. Indeed, the only paragraph in Reichel relating to adenoviral vectors that mentions *ex vivo* therapy teaches away from this approach. Reichel states (at p. 4):

> The development of a gene therapy for diseases of the eyes, especially degeneration of the retina, ***is primarily sensible in vivo*** by means of animal models. For example, the RPE or also the cornea are available *ex vivo* for gene

> transfer because of the possibility for culturing; ***but for diseases of the retina this possibility is not available*** because up to now neither a cell culture nor a transplantation, and above all no re-integration of neurons has been achieved. Thus a way as it has been successfully clinically practiced for example in the case of the amino-deaminase deficiency by ***an ex vivo transfer, cannot be used for inherited degenerations of the retina.***

Thus, Reichel, while recognizing that retinal pigment epithelial cells may be cultured, teaches away from the use of such culture, stating that *ex vivo* therapy for retinal disorders is contraindicated.

Furthermore, with respect to claim 25, Applicants note that this claim requires culturing of transduced pigment epithelial cells of the eye on a feeder layer. Applicants submit that the references do not teach or suggest this culture technique. Reichel, as acknowledged by the Office, does not teach culturing of pigment epithelial cells of the eye in the presence of a feeder layer. Tezel, while disclosing that RPEs may be maintained on tissue culture plates pre-coated with *extracellular matrix*, does not teach or suggest co-cultivation with a feeder layer of cells. Williams, which suggests that maintenance of a stem cell phenotype can be accomplished using fibroblast feeder layers, does not suggest the use of such feeder layers for maintaining pigment epithelial cells of the eye. And Funk discusses the culture of primate pluripotent stem cells in the absence of feeder layers. This reference is cited as teaching that RPE cells are "progenitor cells." Applicants point out that, at col. 17, lines 8-11, Funk distinguishes pluripotent stem cells from committed precursor cells and in this context mentions RPEs as one of the latter types of cells. Thus, Applicants submit that Funk does not teach that RPEs would be considered pluripotent stem cells or that they should be cultured on a feeder layer. For these reasons as well, the rejection of claim 25 should be withdrawn.

In conclusion, Applicants submit that the primary reference Reichel does not support a *prima facie* case of obviousness for the current claims. The disclosure in Reichel concerning administration of conventional non high capacity vectors to retinal

pigment epithelium does not forecast similar success with vectors lacking all adenoviral coding sequences, as currently claimed. Nor does the disclosure of transduction of retinal neurons by subretinal administration of EAMs, in the absence of hindsight, render obvious the presently claimed invention, which is directed to different cells -- pigment epithelial cells of the eye -- transduced with a different and further advanced adenoviral construct. Moreover, Applicants' vectors differ significantly from EAMs in their lack of *E. coli* sequences and genetic homogeneity. Neither this modification from the EAM vector design nor Applicants' superior outcome were suggested or predicted by the Reichel teaching. Finally, nothing in the Reichel reference would lead one skilled in the art to reasonably predict the unexpected and unanticipated finding that adenoviral vectors *lacking all coding sequence* could be used successfully for introduction of foreign genes into pigment epithelial cells of the eye, much less that such vectors would support their characteristic property of long-term expression of such genes. This property of long-term expression need not be recited in Applicants' claims as it is an inherent characteristic of the claimed vectors and can therefore be relied upon for patentability. Indeed, the fact that Applicants' vectors support long-term expression in pigment epithelial cells confirms the fact that Applicants' vectors differ in significant ways from the more conventional vectors described by Reichel.

Moreover, with respect to claims 10 and 25, the obviousness rejection should be withdrawn as the cited references, alone or in combination, do not suggest that *ex vivo* therapy would be appropriate for treating retinal disorders, and therefore cannot motivate the *in vitro* culture of adenoviral-transduced pigment epithelial cells of the eye. Further, the references fail to teach or suggest the use of a feeder layer for accomplishing such *in vitro* culture.

Applicants submit that all § 103 rejections in this case should be withdrawn. Reconsideration is respectfully requested.

Information Disclosure Statement

Applicants note that the Form PTO 1449 that was submitted with an Information Disclosure Statement filed on October 16, 2002 has not been initialed and returned, and hereby request that it be initialed and returned with the next Office action.

Conclusion

Applicants submit that all claims are now in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying to the final Office action for one month, to and including August 4, 2006.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 02 August 2006

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